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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/055,711	REBAR ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,23-28,30-48 and 52-57* is/are pending in the application.

4a) Of the above claim(s) *1,3,5,23,24,33-35,38,42-48 and 52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,25-28,30-32,36,37,39-41 and 53-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 3/24/2008, in which claim 22 was canceled. Currently, claims 1-5, 23-28, 30-48 and 52-57 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant elected Group II (drawn to nucleic acid), species: DNA target sequence, zinc finger component comprising X(3)-Cys-X(2)-Cys-X(12)-His-X(3)-Z-X(4), target located in a plant cell, and a maize C1 activation domain in the replies filed on 8/3/2004 and 11/18/2004. This restriction requirement was made FINAL in the Office action mailed 2/9/2005 and reiterated in the Office action mailed 11/15/2005.

The requirement for the election of a specific zinc finger component, as set forth on pages 3-4 of the Office action mailed 7/1/2004 was withdrawn in the Office action mailed 6/14/2206. The remainder of the species election requirement was maintained in the Office action mailed 6/14/2006. Thus, the species election requirement for target sequence type (DNA), where the target is located (plant cell), and functional domain type (C1 activation domain) are maintained.

Claims 1, 33, 42-48 and 52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the replies filed on 8/3/2004 and 11/18/2004.

Claims 3, 5, 23-24, 34-35 and 38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the replies filed on 8/3/2004 and 11/18/2004.

Currently, claims 2, 4, 25-28, 30-32, 36-37, 39-41 and 53-57 are under consideration.

This application contains claims 1, 33, 42-48 and 52 drawn to an invention nonelected with traverse in the replies filed on 8/3/2004 and 11/18/2004. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Arguments - Claim Objections

The objection of claim 22 is moot in view of Applicant's cancellation of the claim in the reply filed 3/24/2008.

Terminal Disclaimer

The terminal disclaimer filed on 3/24/2008 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patent No. 7,273,923 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Response to Arguments - Double Patenting

The rejection of claims 2, 4, 30-32, 36-37, 39-41 and 56-57 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12-14, 18, 25 and 27 of U.S. Patent No. 7,273,923 has been withdrawn in view of the proper terminal disclaimer.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4, 25-28, 30-32, 36-37, 39-41 and 53-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was made in the Office action mailed 1/2/2008 and has been rewritten to remove portions overcome by Applicant's arguments, filed 3/24/2008.

Claims 2, 4, 25-28, 30-32, 36, 37, 39-41 and 53-55 are drawn to an isolated polynucleotide encoding a non-naturally-occurring zinc-finger binding protein comprising a non-canonical zinc finger component, wherein said non-canonical zinc finger component contains a beta turn comprising two amino-terminal cysteine or histidine zinc coordinating residues and an alpha helix comprising two carboxy-terminal cysteine or histidine zinc coordinating residues, where at least one of the amino-terminal zinc coordinating residues is a histidine residue or at

least one of the carboxy-terminal zinc coordinating residues is a cysteine residue and wherein the recognition region of the zinc-finger binding domain protein is non-naturally occurring and is engineered to bind to a target sequence in a plant cell. Claims 56 and 57 are drawn to an isolated polynucleotide encoding a non-naturally occurring zinc-finger binding protein comprising a non-canonical zinc finger component, wherein said non-canonical zinc finger component contains an amino-terminal beta turn comprising two zinc coordinating cysteine residues, and a carboxy-terminal alpha helix comprising two zinc coordinating residues where one zinc coordinating residue is a cysteine and the other is a histidine, and wherein the protein comprises a non-naturally occurring recognition helix that is engineered to bind to a target sequence. Thus, the claims are drawn to a genus of compounds that is defined by secondary structure (beta turn and alpha helix), primary structure (cysteine and histidine zinc coordinating residues that differ from the canonical C2H2 consensus), and function in that they must be capable of binding to a target sequence that is a protein or nucleic acid sequence. Given the structural limitations of the claims, the primary structure must be capable of providing the information necessary to allow the protein to fold into the recited secondary structures and bind to a target protein or nucleic acid sequence.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In the instant case, while the claims contain a description of a general structure drawn to the non-canonical zinc finger component containing a beta turn comprising the two amino-terminal cysteine and histidine zinc coordinating residues and an alpha helix comprising the two carboxy-terminal cysteine and histidine zinc coordinating residues, the structure is further limited by excluding the C2H2 structure which supports the secondary structure, instead claiming a retention of the structure without use of the standard C2H2 zinc coordinating residues. In other words, what is claimed is a structure where the critical C2H2 residues, which are used to support the secondary structure, have been replaced with amino acid residues that are not C2H2 (and whatever other amino acid changes are needed to support that replacement of the zinc coordinating residue(s)). While cysteine and histidine are both known to coordinate zinc atoms in the context of properly folded zinc fingers, these critical amino acids are not predictably interchanged (Green et al. Biochem J., Vol. 333, pages 85-90, 1998, cited in a prior action). For example, Green et al teach that the conversion of the C2H2 zinc fingers of Zif268 to C4 zinc fingers allows proper folding and function of the Zif268 zinc finger domains only if the mutation is present in zinc finger 1 or 3. In contrast, mutation of zinc finger 2 abolishes binding, which is likely a result of the inability of the protein to form the necessary secondary structure (e.g. Green et al, page 89, paragraph bridging columns). Furthermore, if zinc fingers 1 and 3 were simultaneously mutated, the protein was unable to bind DNA (e.g. Green et al, page 89, paragraph bridging columns). Thus, sequences other than the zinc coordinating residues play a role in determining the secondary structure and target sequence binding of the polypeptide. A review of the specification identified multiple examples of only one general type of non-canonical zinc finger protein meeting the claim limitations: a zinc finger protein in which the

zinc coordinating residues are C2HC. There does not appear to be a description of any other zinc fingers that meet the claim limitations with regard to the zinc coordinating residues and secondary structure. Furthermore, the specification does not describe a structure function correlation for residues that support the formation of the claimed secondary structure when a zinc coordinating residue is altered. Accordingly, in the absence of sufficient recitation of distinguishing characteristics (e.g., specific sequences) drawn to other types of non-canonical zinc fingers which retain the canonical structure using zinc coordinating residues that are neither C2H2 nor C2HC (the only structures whose sequences are specifically described), the specification does not provide adequate written description of the claimed genus which encompasses all non-canonical zinc fingers having the canonical general structure.

The specification envisions the engineering of zinc finger proteins to bind DNA, RNA or protein (e.g., page 6, lines 16-18). The specification envisions the modification of zinc finger proteins by methods known in the art, including those methods taught by US Patent Nos. 6,007,988 and 6,013,453 (cited on the IDS filed 4/15/2003), as well as US Patent No. 5,789,538, WO 95/19431, WO 96/06166, and WO 98/54311 (cited on the IDS filed 5/11/2005). However, each of these references teaches the engineering of zinc finger proteins to bind to nucleic acid. There is no art of record that provides guidance with respect to the design of zinc finger proteins for binding to protein. The examples within the specification are all directed to sequences that provide recognition of a DNA target sequence (e.g., Examples; Table 3). The specification does not describe any recognition region or recognition helix that provides recognition of protein.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in

possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of non-canonical zinc fingers and recognition regions or helices as claimed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18USPQ2d 1016.

"A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004). In the instant case, the specification describes zinc finger proteins that have the C_2HC structure that bind DNA. Description of this species of zinc finger does not predict the operability of other zinc fingers such as C_4, HCH_2, CHH_2, C_2CH, and H_4. Moreover, the specification and prior art only describe alterations of the recognition region or helix of the zinc finger domain that result in binding to a DNA target sequence. Description of these sequences does not allow one to predict those changes that will result in recognition of a protein sequence.

Given the very large genus of polynucleotides encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to structures necessary to confer the claimed secondary structure and binding properties, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention for claims 2, 4, 25-28, 30-32, 36, 37, 39-41 and 53-57.

Response to Arguments - 35 USC § 112

Applicant's arguments, see pages7-11, filed 3/24/2008, with respect to the rejection of claims 2, 4, 22, 25-28, 30-32, 36, 37, 39-41 and 53-57 under 35 U.S.C. 112, second paragraph, have been fully considered and are persuasive. The previous rejection of claims 2, 4, 22, 25-28, 30-32, 36, 37, 39-41 and 53-57 has been withdrawn.

The rejection of claim 22 under 35 U.S.C. 112, first paragraph (written description), is moot in view of Applicant's cancellation of the claim in the reply filed 3/24/2008.

Applicant's arguments, see pages 11-13, filed 3/24/2008, with respect to the rejection of claim 57 under 35 U.S.C. 112, first paragraph (written description) have been fully considered and are persuasive. The previous rejection of claim 57 has been withdrawn.

With respect to the rejection of claims 2, 4, 25-28, 30-32, 36-37, 39-41 and 53-57 under 35 U.S.C. 112, first paragraph (written description), Applicant's arguments filed 3/24/2006 have been fully considered but they are not persuasive.

The remarks directed to "non-naturally occurring" zinc finger domains have been considered and are found persuasive. This portion of the rejection has been removed.

The response does not specifically address the lack of description for non-canonical zinc finger components other than CCHC zinc finger domains. The response does not specifically address the design of zinc finger proteins for binding to protein target sequence.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 4, 25-28, 30-32, 36-37, 39-41 and 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 7,151,201 B2, cited in a prior action; see

the entire reference) in view of Green et al (Biochem J., Vol. 333, pages 85-90, 1998, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 1/2/2008 and is reiterated below.

Barbas, III et al teach nucleic acid molecules encoding zinc finger proteins that bind to a target nucleotide sequence of 3, 6, 9, 12, 15 or 18 nucleotides, where the zinc finger protein binds the target nucleotide sequence of the formula $(GNN)_n$, where N is any one of A, T, C or G and n is an integer from 1 to 6 (e.g., column 3, lines 13-43; column 18, lines 48-64; column 19, lines 53-57; Table 2). Barbas, III et al teach that the target nucleotide sequence can be present in a plant cell and can be a promoter sequence (e.g., column 3, lines 23-50). Specific plant promoter sequences disclosed by Barbas, III et al include GCG target DNA sequences (e.g., Examples 2 and 3). Barbas, III et al teach that the encoded zinc finger protein also includes an activation domain of a regulatory protein, such as a C1 activator domain of maize, in order to activate expression of the target gene operably linked to the target nucleotide sequence (e.g., column 4, lines 42-48; column 25, lines 10-46). Barbas, III et al teach that the Zif268 protein is a useful zinc finger framework for making modifications to the zinc finger protein, where positions in the alpha-helix (-1, 3 and 6) are involved in specific base contacts (e.g., column 21, lines 8-39). Barbas, III et al teach expression vectors comprising the polynucleotide sequences encoding the zinc finger proteins, and plant host cells comprising the vectors (e.g., column 32, lines 10-36). Barbas, III et al teach the suspension of the polynucleotides in a pharmaceutically acceptable excipient that is an electroporation buffer of 0.3 M mannitol, 5 mM MES, 70 mM KCl, pH 5.8 (e.g., column 55, lines 35-67).

Barbas, III et al do not teach the isolated polynucleotide, where the polynucleotide encodes a non-canonical zinc finger component comprising two amino-terminal zinc coordinating cysteine residues and an alpha helix comprising two carboxy-terminal zinc coordinating cysteine residues.

Green et al teach an isolated polynucleotide encoding a modified zif268 zinc finger binding protein, which contains a mutation of the C2H2 motif to a C_4 motif in the first or third zinc finger (e.g. page 87, Results). In the C_4 motif of Green et al, the zinc coordinating residues are two amino-terminal cysteine residues and two carboxy-terminal cysteine residues, and thus at least one of the carboxy-terminal zinc coordinating residues is a cysteine. The modified zif268 zinc finger binding proteins are engineered to bind to the wild type zif268 target DNA sequence 5'-GCGTGGGCG-3' (e.g. paragraph bridging pages 87-88; page 87, right column, 1st full paragraph; Figure 2, especially lanes c and e). Green et al teach that the mutations allowed for proper folding of the zinc fingers to form a beta turn comprising two amino-terminal zinc coordinating cysteine or histidine residues and an alpha helix comprising two carboxy-terminal zinc coordinating cysteine or histidine residues, which is indirectly evidenced by the ability of the expressed protein to bind DNA (e.g. paragraph bridging pages 88-89). Thus, Green et al indirectly provide evidence that the modified zif268 proteins comprise a non-canonical zinc finger component that contains a beta turn and an alpha helix that coordinate zinc using the four cysteine residues.

Because both Barbas, III et al and Green et al disclose zinc finger domains capable of binding a GCG triplet nucleic acid target sequence, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the GCG-binding zinc

finger domain of Barbas, III et al with the C_4 CGC-binding zinc finger domain of Green et al in the context of a three finger polypeptide where the C_4 zinc finger is the first or third zinc finger or in the context of a zinc finger containing four, five or six zinc fingers, where the C_4 zinc finger is the first zinc finger, to achieve the predictable result of making a polynucleotide that encodes a zinc finger polypeptide that binds to a plant promoter sequence containing a GCG triplet.

Claims 2, 4, 25-28, 30-32, 36, 39-41 and 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 6,242,568, cited as reference A39 on the IDS filed 5/11/2005; see the entire reference) in view of Green et al (Biochem J., Vol. 333, pages 85-90, 1998, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 1/2/2008 and is reiterated below.

Barbas, III et al teach polynucleotides encoding zinc finger-nucleotide binding polypeptides in combination with a pharmaceutically acceptable carrier (e.g., column 2, line 66 to column 3, line 17; column 4, lines 48-65; column 7, line 56 to column 8, line 54). Barbas, III et al teach recombinant expression vectors comprising the polynucleotides, and host cells such as plant cells comprising the vectors (e.g., column 18, line 47 to column 20, line 56; column 26, lines 38-46). Barbas, III et al teach that the zinc finger binding motif (i.e., target nucleic acid sequence) can be any sequence designed by the experiment or to which the zinc finger protein binds, and the motif may be found in any DNA or RNA sequence, including regulatory sequences such as a promoter sequence (e.g., column 5, line 11 to column 6, line 62). The target nucleotide sequence may be a sequence in a plant cell, whether it is a plant nucleotide sequence or a sequence that is not naturally occurring in the cell (e.g., column 5, lines 52-65; column 7,

lines 40-48; column 26, lines 38-46). Barbas, III et al teach that the encoded zinc finger protein can be a variant, mutagenized protein and/or an expanded zinc finger protein having as many as 12 zinc fingers, which will bind a sequence of up to 36 contiguous base pairs (e.g., paragraph bridging columns 4-5; column 7, lines 20-55). Barbas, III et al teach that zif268 is a zinc finger protein that can be mutagenized and/or expanded (e.g., column 7, lines 40-55). Barbas et al specifically teach variants of zif268 zinc fingers that bind to the triplets GCG, TGT, TGG, TTG, and CTG (e.g., Figure 9). Further, Barbas, III et al teach embodiments where the polynucleotides encode the zinc finger-nucleotide binding polypeptides that are transcriptional activators in plants, and thus contain an activation domain (e.g., column 26, lines 38-58).

Barbas, III et al do not teach the isolated polynucleotide, where the polynucleotide encodes a non-canonical zinc finger component comprising two amino-terminal zinc coordinating cysteine residues and an alpha helix comprising two carboxy-terminal zinc coordinating cysteine residues.

Green et al teach an isolated polynucleotide encoding a modified zif268 zinc finger binding protein, which contains a mutation of the C2H2 motif to a C_4 motif in the first or third zinc finger (e.g. page 87, Results). In the C_4 motif of Green et al, the zinc coordinating residues are two amino-terminal cysteine residues and two carboxy-terminal cysteine residues, and thus at least one of the carboxy-terminal zinc coordinating residues is a cysteine. The modified zif268 zinc finger binding proteins are engineered to bind to the wild type zif268 target DNA sequence 5'-GCG TGG GCG-3' (e.g. paragraph bridging pages 87-88; page 87, right column, 1st full paragraph; Figure 2, especially lanes c and e). Thus, Green et al teach a non-canonical zinc finger domain that binds to the sequence GCG when it is the first or third zinc finger. Green et al

teach that the mutations allowed for proper folding of the zinc fingers to form a beta turn comprising two amino-terminal zinc coordinating cysteine or histidine residues and an alpha helix comprising two carboxy-terminal zinc coordinating cysteine or histidine residues, which is indirectly evidenced by the ability of the expressed protein to bind DNA (e.g. paragraph bridging pages 88-89). Thus, Green et al indirectly provide evidence that the modified zif268 proteins comprise a non-canonical zinc finger component that contains a beta turn and an alpha helix that coordinate zinc using the four cysteine residues.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide encoding a zinc finger-nucleotide binding polypeptide of Barbas, III et al to include the non-canonical C_4 zinc finger domain that recognizes GCG of Green et al in the context of a three finger polypeptide where the C_4 zinc finger is the first or third zinc finger, or in the context of a zinc finger containing up to 12 zinc fingers where the C_4 zinc finger is the first zinc finger, to achieve the predictable result of making a polynucleotide that encodes a zinc finger polypeptide that binds to a plant promoter sequence containing a GCG triplet.

One would have been motivated to include the C_4 CGC-binding zinc finger domain of Green et al in order to expand the repertoire of available zinc finger nucleotide-binding proteins encoded by the polynucleotides. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (US Patent No. 6,242,568, cited as reference A39 on the IDS filed 5/11/2005; see the entire reference) in view of Green et al (Biochem J., Vol. 333, pages 85-90, 1998, cited in a prior action; see the entire reference) as applied to claims 2, 4, 25-28, 30-32, 36, 39-41 and 53-55 above, and further in view of Guyer et al (Genetics, Vol. 149, pages 633-639, 1998, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 1/2/2008 and is reiterated below.

The combined teachings of Barbas, III et al and Green et al are described above and applied as before.

Barbas, III et al and Green et al do not teach the polynucleotide where the activation domain is a maize C1 activation domain.

Guyer et al teach *Arabidopsis* plants comprising a stably integrated hybrid transcription factor, and plants comprising an activatable transgene, where the hybrid transcription factor and activatable transgene are brought together in the same cell by fertilization (e.g. paragraph bridging pages 633-634). Specifically, Guyer et al teach a GAL4 DNA binding domain fused to a maize C1 transcription activation domain as the hybrid transcription factor, and a reporter transgene controlled by a synthetic promoter comprising ten GAL4 DNA binding sites (e.g. paragraph bridging pages 633-634; Figure 1). Further, Guyer et al teach that many positive transcriptional regulatory factors are modular, consisting of a DNA-binding domain and an activation domain and that fusing combinations of these elements derived from different kingdoms results in the production of diverse hybrid factors having defined DNA-binding specificity and transcriptional activation function with advantages over expression under direct

control by a natural promoter (e.g. page 633, left column; page 638, paragraph bridging columns).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the polynucleotide to comprise a C1 activation domain taught by Guyer et al because Barbas, III et al teach it is within the skill of the art to make a plant cell comprising the polynucleotide where the polynucleotide encodes a zinc finger-nucleotide binding polypeptide that activates expression of a gene operably linked to the target nucleotide sequence, and Guyer et al teach that the maize C1 activation domain functions in a plant cell to activate transcription from a heterologous DNA binding domain.

One would have been motivated to specifically use the maize C1 activation domain, because it was known in the art to function in plants. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

The rejection of claim 22 under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al in view of Green et al is moot in view of Applicant's cancellation of the claim in the reply filed 3/24/2008.

With respect to the rejections based upon the application of the Barbas, III et al and Green et al references under 35 U.S.C. 103(a), Applicant's arguments filed 3/24/2008 have been fully considered but they are not persuasive.

The response asserts that the pending claims require that at least one of the two amino terminal zinc coordinating residues is a His residue and at least one of the two carboxy terminal zinc coordinating residues be a Cys residue. The response asserts that the proteins must be CHCC, CHHC, CHCH, HCCC, HCHC, CHCH, HHCH, HHHC, or HCCH. Based upon this interpretation of the claim, the response asserts that Barbas and Green fail to teach non-canonical zinc finger domains encompassed by the claims. The response asserts that the CCCC zinc finger of Green does not meet the limitations of the pending claims. This is not found persuasive, because the claims require "at least one of the amino-terminal zinc coordinating residues is a histidine residue, or at least one of the carboxy-terminal zinc coordinating residues is a cysteine residue" (emphasis added). Thus, the claims encompass embodiments where the amino-terminal zinc coordinating residues are both cysteine, and at least one of the carboxy-terminal zinc coordinating residues is a cysteine. Thus, the CCCC (Cys4) zinc fingers of Green et al meet the limitations of the claims as currently written.

The response asserts that the Office has failed to provide evidence that the claimed invention is a predictable use of the prior art elements according to their established functions. This is not found persuasive, because the evidence is provided by Green et al. Green et al teach the context in which the Cys4 zinc fingers are capable of binding DNA, and this context is not altered by the combination of Barbas, III et al and Green et al. Green et al teach that the Cys4 zinc finger is tolerated at finger 1 or finger 3 of a three finger protein. Cys4 is not tolerated at finger 2 and is not tolerated when both fingers 1 and 3 are Cys4 (e.g., page 89, left column, Discussion). Green et al provide evidence of binding of the non-canonical zinc finger (e.g., paragraph bridging pages 87-88; page 88, right column). The response asserts that Green's

failure to teach function of the zinc finger proteins *in vivo* would prevent one of skill in the art from combining the teachings of Barbas, III et al and Green et al. This is not found persuasive, because Green et al teach functional binding *in vitro* of the zinc finger proteins comprising non-canonical zinc finger domains (e.g., paragraph bridging pages 87-88; page 88, right column). The response does not provide any evidence that it is unpredictable to extrapolate *in vitro* binding function to *in vivo* binding function. The present specification teaches that zinc finger proteins are designed and selected by processes such as phage display, which are based upon *in vitro* binding and not *in vivo* binding (e.g., page 10, lines 17-29). The prior art cited by Applicant in the present specification teaches that it is routine in the art to determine binding function *in vitro* for *in vivo* applications (e.g., US Patent No. 6,007,988, cited on the IDS filed 4/15/2003; see the abstract and column 11, lines 5-47). Thus, it would not be unpredictable to use the non-canonical zinc fingers of Green et al in the manner taught by Green et al for binding *in vivo* as taught by Barbas, III et al.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached at 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
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